UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY

AND POLLUTION PREVENTION

MEMORANDUM

DATE: May 30, 2012

SUBJECT: Tefluthrin: Report of the Cancer Assessment Review Committee

PC Code: 128912
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: Cancer Assessment
TXR No.: 0056340
MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A

CAS No.: N/A
40 CFR: N/A

FROM: Jess Rowland, Co-Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Stephen Dapson, Toxicologist
RAB 6, Health Effects Division (7509P)

BeWanda Alexander, RM
Richard Gebken, PM
Insecticide Branch, Registration Division (7505P)

The Cancer Assessment Review Committee met on January 11, 2012 to evaluate the cancer classification of Tefluthrin in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

TEFLUTHRIN

PC Code: 128912

Final

May 30, 2012

CANCER ASSESSMENT REVIEW COMMITTEE

HEALTH EFFECTS DIVISION

OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: Stephen Dapson, Toxicologist

DOCUMENT PREPARATION: Jess Rowland, Co-Chair

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Jonathan Chen

Marion Copley

Kit Farwell

Ray Kent

Nancy McCarroll

P.V. Shah

Charles Wood

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist

OTHER ATTENDEES: Khin Oo (HED), Jenny Tao (AD), Michelle Centra (AD)

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EXECUTIVE SUMMARY

On January 11, 2012, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) evaluated the carcinogenic potential of tefluthrin. This was the first CARC meeting for this chemical.

The data were presented to the CARC by Dr. Stephen Dapson of Risk Assessment Branch 6. In a combined chronic toxicity/carcinogenicity study with Alpk:AP rats (64/sex/group), tefluthrin was administered in the diet at 0, 25, 100 or 400 ppm for 104 weeks. Doses were equivalent to 0, 1.1, 4.6 or 18.2 mg/kg/day, respectively. An additional 12 rats per sex per dose were designated for interim sacrifice at week 52. In a carcinogenicity study with SPF Alpk:AP mice (50/sex/group), tefluthrin was administered in the diet at 25, 100 or 400 ppm for 104 weeks; a control group (100/sex) received the basic diet for 104 weeks. Doses were equivalent to 0, 3.4, 13.5 or 54.4 mg/kg/day, respectively. Dr. Dapson also discussed the toxicology, metabolism and mutagenicity studies as well as structure-activity relationships.

The CARC did <u>not</u> consider the uterine tumors seen in female rats to be treatment-related. In female rats, there was a significant trend ($p<0.05$) for uterine adenocarcinomas. However, there were no significant pair-wise comparisons of the dosed groups with the controls. The incidences of this tumor at all dose groups was within the historical control range (0-15%) provided by the registrant. Additionally, there were no corroborative non-neoplastic lesions. There was no evidence of carcinogenicity in male rats. The dose levels tested were adequate to assess the carcinogenicity of tefluthrin in rats based on the clinical signs of neurotoxicity and changes in the body weight/body weight gains observed at the high dose in both sexes.

The CARC did <u>not</u> consider the pituitary gland tumors seen in both male and female mice to be treatment-related. Male mice had statistically significant trends in pituitary gland adenomas and combined adenomas and/or carcinomas, both at $p < 0.05$. However, there were no significant pair-wise comparisons of the dosed groups with the controls. Female mice had statistically significant trend in pituitary gland pars intermedia adenomas at $p < 0.05$ and a statistically significant trend in pituitary gland pars intermedia combined adenomas and/or carcinomas at $p < 0.01$. There was a statistically significant pair-wise comparison of the 400 ppm dose group with the controls for pituitary gland pars intermedia combined adenomas and/or carcinomas at $p < 0.05$. The incidence of carcinomas at 400 ppm was low (a single carcinoma). Additionally, there were no corroborative non-neoplastic pituitary lesions (hypertrophy/ hyperplasia) to indicate that the tumors were treatment related. The dose levels tested were adequate to assess the carcinogenicity of tefluthrin in mice based on the decreased body weight and body weight gain (both sexes) and the presence of non-neoplastic lesions in the uterus and liver (both sexes) observed at the high dose level.

Based on the negative results from a battery of genetic toxicology assays, there is no concern for mutagenicity. Also, tefluthrin has no structural features that would either raise or diminish concern for carcinogenicity.

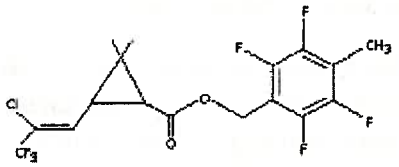
In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC determined that tefluthrin in "Not Likely to be Carcinogenic to Humans." This classification is based on the lack of evidence of carcinogenicity in male and female mice and

male and female rats, and the lack of evidence of mutagenicity. The quantification of cancer risk is not required.

I. INTRODUCTION

On January 11, 2012, the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to evaluate the carcinogenic potential of tefluthrin.

II. BACKGROUND INFORMATION

Test Compound Nomenclature.	
Compound	
Common name	Tefluthrin
Molecular formula	$C_{17}H_{14}ClF_7O_2$
Molecular weight	418.74
Company experimental name	R151993
IUPAC name	2,3,5,6-tetrafluoro-4-methylbenzyl (1*RS*)-*cis*-3-[(*Z*)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate
CAS name	(2,3,5,6-tetrafluoro-4-methylphenyl)methyl (1*R*,3*R*)-*rel*-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate
CAS registry number	79538-32-2
End-use product (EP)	Force® SB (EPA File Symbol 100-RGAR)

The currently registered formulations of tefluthrin include granules and an emulsifiable concentrate (EC) applied at-planting for the control of soil insect pests of corn. There is also an EC registered for treatment of corn seed in commercial seed treatment facilities.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Reference: Stonard, M. (1986) Tefluthrin: 2 Year Feeding Study in Rats: Laboratory Project ID: CTL/P/1522. Unpublished study prepared by ICI Central Toxicology Laboratory. MRID No. 40141307.

A. Experimental Design: In a combined chronic toxicity/carcinogenicity study with Alpk:AP rats (64 rats/sex/group), tefluthrin was administered in the diet at 0, 25, 100 or 400 ppm for 104 weeks. Doses were equivalent to 0, 1.1, 4.6 or 18.2 mg/kg/day, respectively. An additional 12 rats per sex per dose were designated for interim sacrifice at week 52.

B. Survival Analyses: Treatment had no adverse effect on survival in either sex. As shown in Table 1, there were no survival disparities among the dose groups for female rats.

Table 1. Tefluthrin – Alpk:AP Rat Study (MRID No. 40141307)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results						
Dose (ppm)	**Study Weeks**					
	1-26	27-52	52[I]	53-78	79-104[f]	Total
0	1/76	2/75	12/73	7/61	20/54	30/64 (47)
25	0/64	0/64	12/64	6/52	18/46	24/52 (46)
100	0/64	1/64	11/63	7/52	21/45	29/53 (55)
400	8/76	3/68	9/65	6/56	21/50	38/67 (57)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[f]Final sacrifice at week 104 .
[I]Interim sacrifice at week 52.
Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.

C. Discussion of Tumor Data

Female rats had a statistically significant trend ($p < 0.05$) in uterine adenocarcinomas, however, there were no significant pair-wise comparisons of the dosed groups with the controls. The statistical analyses of the tumors in the female rats were based upon Fisher's Exact Test for pair-wise comparisons and the Exact Test for trend (Table 2).

The incidence of this tumor was within the historical control range (0-15%) provided by the registrant.

Table 2. Tefluthrin - Alpk:AP Rat Study (MRID No. 40141307)

Female Uterine Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results				
Lesion	**0 ppm**	**25 ppm**	**100 ppm**	**400 ppm**
Adenocarcinomas#	2[a]/60	0/52	2/52	5/56
(%)	(3)	(0)	(4)	(9)
p =	0.02439*	1.0000	0.63498	0.19176

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53.
#No adenomas were observed.
[a]First adenocarcinoma observed at week 75, dose 0 ppm.
Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

D. Non Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen in female or male rats at any dose level.

E. *Adequacy of the Dosing for Assessment of Carcinogenicity*

The committee concluded that the dose levels tested were adequate to assess the carcinogenicity of tefluthrin in rats based on the clinical signs of neurotoxicity and changes in the body weight/body weight gains observed at the high dose in both sexes. Clinical signs of neurotoxicity at 400 ppm included an increased response to sound, increased activity, tremors, abnormal gait, including splayed gait, in both sexes. Body weight gain was reduced in rats at 400 pm from the first week of the study. Initially, females were more severely affected but the body weights continued to diverge from control values in both sexes for the first 6 months of the study. The maximum reduction during this time period was approximately 7 and 10% below control values for males and females, respectively. In females at 400 ppm, body weight gains were suppressed throughout the study with final body weights approximately 11% lower than those of the controls. From week 80, male body weights in the 400 ppm group were comparable to control values.

2. Carcinogenicity Study in Mice

Reference: Wickramaratne, G. (1986) Tefluthrin: Lifetime Feeding Study in Mice: Laboratory Project ID: CTL/P/1509. Unpublished study prepared by ICI Central Toxicology Laboratory. MRID No: 40161106

Clapp, M. (1988) Tefluthrin: Lifetime Feeding Study in Mice--Supplemental Data on Organ Weights and Organ to Bodyweight Ratios: Laboratory Project ID: CTL/P/1509. Unpublished study prepared by ICI Central Toxicology Laboratory. MRID No.: 40883403

A. *Experimental Design:* In a carcinogenicity study with SPF Alpk:AP mice (50 mice/sex/group) were fed diets containing tefluthrin at dose levels of 25, 100 or 400 ppm of Tefluthrin for 104 weeks; a control group (100/sex) received the basic diet for 104 weeks. Doses were equivalent to 0, 3.4, 13.5 or 54.4 mg/kg/day, respectively.

B. *Survival Analyses:* There were no survival disparities among the dose groups for male or female (Tables 3 and 4).

Table 3. Tefluthrin – SPF Alpk:AP Mouse Study (MRID No. 40161106)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results					
Dose (ppm)	**Study Weeks**				
	1-26	27-52	53-78	79-104[†]	Total
0	4/100	5/96	18/91	40/73	67/100 (67)
25	4/50	4/46	5/42	16/37	29/50 (58)
100	1/49[a]	3/48	8/45	22/37	34/49 (69)
400	1/50	5/49	13/44	15/31	34/50 (68)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval. [†]Final sacrifice at week 104.
[a]One accidental death at week 1, dose 100 ppm.
( ) Percent.
Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.

Table 4. Tefluthrin – SPF Alpk:AP Mouse Study (MRID No. 40161106)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results					
Dose (ppm)	**Study Weeks**				
	1-26	27-52	53-78	79-104[f]	Total
0	1/98[a]	7/97	14/90	49/76	71/98 (72)
25	2/50	2/48	14/45[b]	19/31	37/49 (76)
100	0/50	1/50	14/49	23/35	38/50 (76)
400	2/50	3/48	9/45	27/36	41/50 (82)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[f]Final sacrifice at week 104.
[a]Two accidental deaths, one each at weeks 9 and 11, dose 0 ppm.
[b]One accidental death at week 63, dose 25 ppm.
( ) Percent.
Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

C. Discussion of Tumor Data

Male mice had statistically significant trends in pituitary gland adenomas and combined adenomas and/or carcinomas, both at $p < 0.05$. However, there were no significant pair-wise comparisons of the dosed groups with the controls. The statistical analyses of the tumors in the male mice were based upon Fisher's Exact Test for pair-wise comparisons and the Exact Test for trend (Table 5).

Female mice had a statistically significant trend in pituitary gland pars intermedia adenomas at $p < 0.05$. There was also a statistically significant trend in pituitary gland pars intermedia combined adenomas and/or carcinomas at $p < 0.01$. A statistically significant pair-wise comparison of the 400 ppm dose group with the controls was seen for pituitary gland pars intermedia combined adenomas and/or carcinomas at $p < 0.05$. The statistical analyses of the tumors in the female mice were based upon Fisher's Exact Test for pair-wise comparisons and the Exact Test for trend (Table 6). It is noted that current pathology guidelines do not distinguish the pituitary gland in general from the pars intermedia.

No historical control data were submitted for the mouse tumors.

Table 5. Tefluthrin – SPF Alpk:AP Mouse Study (MRID No. 40161106)

Male Pituitary Gland Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results				
Lesions	**0 ppm**	**25 ppm**	**100 ppm**	**400 ppm**
Adenomas (%) p =	2/80 (3) 0.0196*	0/29 (0) 1.0000	2/33 (6) 0.3333	4[a]/36 (11) 0.0736
Carcinomas (%) p =	0/80 (0) 0.7978	0/29 (0) 1.0000	1[b]/33 (3) 0.2920	0/36 (0) 1.0000
Combined (%) p =	2/80 (3) 0.0231*	0/29 (0) 1.0000	3/33 (9) 0.1478	4/36 (11) 0.0736

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
[a]First adenoma observed at week 78, dose 400 ppm.
[b]First carcinoma observed at week 90, dose 100 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 6. Tefluthrin – SPF Alpk:AP Mouse Study (MRID No. 40161106)

Female Pituitary Gland Pars Intermedia Tumor Rates[+] and Fisher's Exact Test and Exact Trend Test Results				
	0 ppm	25 ppm	100 ppm	400 ppm
Adenomas (%) p =	0/79 (0) 0.0380*	0/41 (0) 1.0000	0/43 (0) 1.0000	2[a]/40 (5) 0.1111
Carcinomas (%) p =	0/79 (0) 0.1970	0/41 (0) 1.0000	0/43 (0) 1.0000	1[b]/40 (3) 0.3361
Combined (%) p =	0/79 (0) 0.0072**	0/41 (0) 1.0000	0/43 (0) 1.0000	3/40 (8) 0.0361*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 52.
[a]First adenoma observed at week 84, dose 400 ppm.
[b]First carcinoma observed at week 86, dose 400 ppm.
Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

D. Non-Neoplastic Lesions

As shown in Table 7, there were dose-related increases in hemangiomatous changes in the uterus at the mid and high dose groups. In the liver, an increase an in hepatic necrosis in females was seen at the mid and high dose, and an increase in telangiectasis was noted in females at the high dose.

Table 7. Tefluthrin – SPF Alpk:AP Mouse Study (MRID No. 40161106)

Non-Neoplastic Lesions in Female Mice				
Tissue/Lesion	**0 ppm**	**25 ppm**	**100 ppm**	**400 ppm**
Uterus: Hemangiomatous changes	3/99	0/49	3/50	6/48 p = 0.002
Liver: Necrosis	2/100	2/49	4/50	5/50 p = 0.002
Liver: Telangiectasis	0/100	1/49	0/50	3/50 p = 0.004

D. Adequacy of Dosing for Assessment of Carcinogenicity

The committee concluded that the dose levels tested were adequate to assess the carcinogenicity of tefluthrin in mice based on the decreased body weight and body weight gain in both sexes and non-neoplastic lesions of the uterus and liver (both sexes) observed at the high dose level as presented in Appendix 3.

IV. TOXICOLOGY

1. Metabolism

It is generally understood that the metabolism of pyrethroids is a detoxifying event; only the parent chemicals are capable of binding the target site for pyrethroid toxicity, *i.e.* axonal sodium channels. Metabolism is predominated by two mechanisms, hydrolysis and oxidation. Trans-isomers are hydrolyzed by carboxyesterases (CaEs) and cis-isomers are oxidized by hepatic P450 enzymes. However, trans-isomers are also subject to metabolism by hepatic enzymes as well.

In a study with rats, radioactivity levels in blood and selected tissues were measured 24 hours after 14 days of repeated daily oral administration of ^{14}C PP993 (Tefluthrin; 1 mg/kg/day). Tefluthrin was rapidly absorbed in rats after single or repeat oral dosing with the radiolabel, and mostly concentrated in the liver. Peak levels of radioactivity in blood and the selected tissues were measured 24 hours after the 14th dose of ^{14}C PP993 (Tefluthrin). The highest levels at 24 hours post-exposure, were found in liver and fat (1.49 and 1.34 µg equivalents PP993 (Tefluthrin)/gm, respectively). The radioactivity levels in bone, brain, heart, muscle, lung and spleen were comparable to or below the mean level found in blood at the same time interval.

The elimination of radioactivity from liver was more rapid than that from any of the other selected tissues (t½=4.8 days) while the elimination rate from fat was the slowest (t½=13.3 days). In comparison, the elimination t1/2 for blood was 10.6 days. The radioactivity was eliminated from blood and tissues by a first order process.

In rats, urinary and fecal metabolic profiles, determined by TLC, were not significantly affected by the number of PP993 (tefluthrin) dosages administered. In other studies with rats and dogs, urine, feces and bile were collected from excretion balance studies in rats and urine from an excretion balance study in dogs were examined for possible biotransformation products of PP993 (tefluthrin). No unchanged PP993 (tefluthrin) was found in either bile or urine; however, a large proportion of radioactivity found in feces was associated with unchanged PP993 (tefluthrin).

An excretion balance study in rats showed that the rates and routes of elimination of radioactivity following a single oral dose (1mg/kg) of ^{14}C acid-labeled PP993 (tefluthrin) or ^{14}C alcohol-labeled PP993 (tefluthrin) were similar, however, the present study showed that the urinary metabolic profiles were different. Metabolites uniquely associated with the acid or alcohol labels indicated that ester cleavage had occurred. Data in this study also suggested that oxidation of PP993 (tefluthrin) may precede ester cleavage. For example, 3 of the 4 identified metabolites in rat feces were found with the ester bond intact, however, oxidation had occurred in the aliphatic groups of the alcohol and/or acid moiety.

Most of the metabolites identified in urine were conjugated, however, two were identified as free metabolites of PP993 (tefluthrin). Two of the major urinary metabolites, identified after the oral administration of ^{14}C alcohol-labeled PP993 (tefluthrin) to rats, were also found in bile. The evidence in this study indicated that PP993 (tefluthrin) was metabolized by oxidation of the acid and alcohol moieties and by ester cleavage.

In a study with dogs, a single low oral (gavage) dose of tefluthrin was rapidly (within the first hour) absorbed in a similar pattern to that observed in rats. Approximately 30% of the administered ^{14}C PP993 (tefluthrin) was absorbed during this study on the basis of radioactivity levels 25-27% in urine as well as those levels measured in blood (peaked at 4-8 hours after dosing) and selected tissues (liver, kidneys, fat). The rate of excretion in dogs was similar between males and females. Residual radioactivity was measured in liver (1.6 and 1.5% of the given dose in males and females, respectively) and to lesser extent in kidney and fat tissues. Radioactivity in blood peaked at levels that varied between 0.27 and 0.62 µg equivalents PP993 (tefluthrin)/gm blood at 4 to 8 hrs after dosing.

2. Mutagenicity

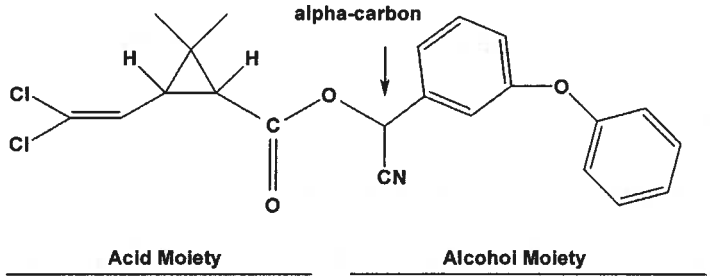
As shown below, tefluthrin was not mutagenic in a series of *in vitro* and *in vivo* assays (TXR No. 0005976).

Assay Type	Concentrations Tested	Results
Salmonella *typhimurium*, TA1535, TA1537, TA1538, TA98, TA100	MRID 40161113 (1987) Acceptable 0, 1.6, 8.0, 40, 200, 1000 or 5000 µg/plate with and without metabolic activation	Negative for reverse mutation up to a precipitating level (5000 µg/plate)
L5178Y/TK Forward mutation assay in mammalian cells (*in vitro)*	MRID 40141314 (1986) Acceptable 0, 250, 500, 1000, 2000 or 4000 µg/mL with and without metabolic activation	Negative up to severe cytotoxicity (8% relative survival at 4000 µg/mL)
UDS assay in rat hepatocyte (*in vitro)*	MRID 40141317 (1986) 0, 10^{-2} to 10^{-9}M	Negative up to severe cytotoxic doses ($\geq 10^{-4}$ M)
Rat BM Cytogenetics (*in vivo*)	MRID 40141316 (1985) 0, 2.5, 12.5 or 25 mg/kg once via oral gavage	Negative for chromosomal damage up to a dose causing a reduction in the mitotic index (25 mg/kg)
Mouse Micronucleus (*in vivo*)	MRID 40141315 (1985) Unacceptable 0, 31 or 50 mg/kg via intraperitoneal injection	Negative but no clinical signs or bone marrow cytotoxicity
Mouse dominant lethal (*in vivo*)	MRID 40141313 (1985) 0, 1, 3 or 10 mg/kg/day via oral gavage for 5 days	Negative up to a dose causing a significant decrease in body weight (10 mg/kg/day)

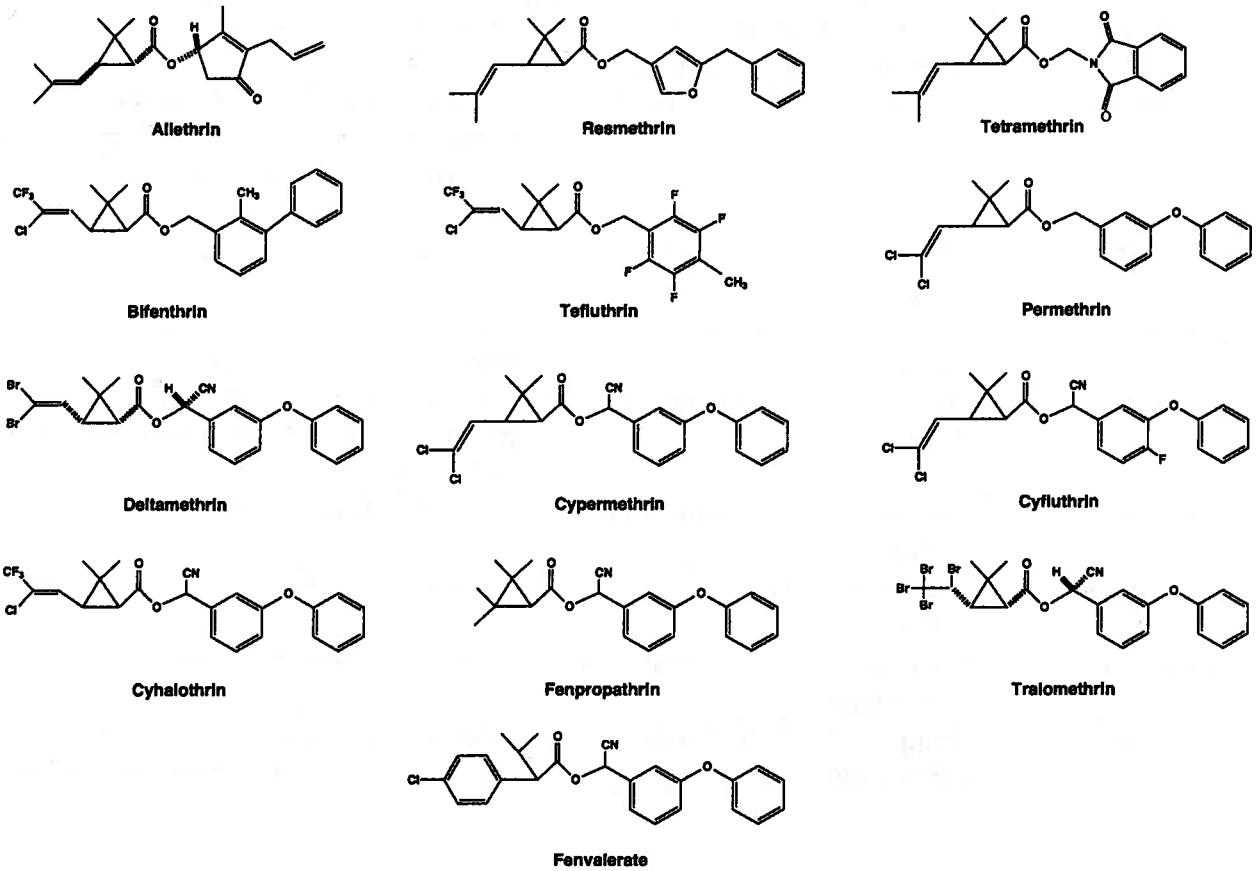
3. Structure-Activity Relationship

Tefluthrin belongs to the pyrethroid class of insecticides. Pyrethroids, the synthetic derivatives of the pyrethrins, have evolved structurally over the past several decades. However, the basic components of pyrethrins, a chrysanthamic acid linked to an aromatic alcohol through an ester linkage have been conserved (Fig. 1). Structural modifications such as the addition of halogens to the chrysanthamic acid and aromatic alcohol moieties and the addition of the α-cyano group have increased photostability, insecticidal potency, and in some incidences, stereoisomerism of the pyrethroids. As a point of reference, pyrethroids lacking the α-cyano group are referred to as Type I and those with the α-cyano group are referred to as Type II pyrethroids. Overall, tefluthrin has no structural features that would either raise or diminish concern for carcinogenicity.

Figure 1. Typical structure of a pyrethroid pesticide including acid and alcohol moieties and location of the alpha-cyano group when present. Cypermethrin is illustrated below.



The pharmacokinetic properties of pyrethroids are greatly influenced by structure and configuration. Pyrethroids typically contain 2 or 3 chiral centers resulting in several structural isomers. Metabolism of the isomers occurs through 2 competing pathways: hydrolysis for trans-isomers, and oxidation for the cis-isomers.



Cancer Classification of Structurally Related Chemicals

Chemical	Classification	Basis for Classification
Bifenthrin	Group C--Possible Human Carcinogen	Urinary bladder & Liver tumors in male and Lung tumors in female Swiss Webster mice. (RfD) approach for quantification of human risk.
Bioallethrin	Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential	Kidney tumors in male Sprague-Dawley rats.
Cyfluthrin	Not Likely to Be Carcinogenic to Humans	No treatment-related tumors
Cypermethrin/ Zeta cypermethrin	Group C--Possible Human Carcinogen	Lung tumors in female Swiss mice. No quantification.
Deltamethrin	Not Likely to Be Carcinogenic to Humans	No treatment-related tumors
Esbiothrin	Suggestive Evidence of Carcinogenicity, but Not Sufficient to Assess Human Carcinogenic Potential	Kidney tumors in male Sprague-Dawley rats.
Esfenvalerate/ Fenvalerate	Group E--Evidence of Non-carcinogenicity for Humans	No treatment-related tumors
Etofenprox	Not Likely Below a Defined Dose Range	Thyroid tumors in male and female Sprague-Dawley rats. Established a thyroid hormone disruption mode of action for thyroid tumors.
Fenpropathrin	Not Likely to be Carcinogenic to Humans	No treatment-related tumors
Permethrin	Likely to be Carcinogenic to Humans	Lung tumors in female, liver and lung tumors in male and female in CD-1 mice
Resmethrin	Likely to be Carcinogenic to Humans	Liver tumors in female Sprague-Dawley rats and Liver tumors in male Swiss Mice. Q1* = 5.621 E-2 (3/4)
Prallethrin	Not Likely to Be Carcinogenic to Humans	No treatment-related tumors
Sumithrin	Not Likely to Be Carcinogenic to Humans	No treatment-related tumors
Tau-fluvalinate	Not Likely To Be Carcinogenic To Humans	No treatment-related tumors
Tetramethrin	Group C--Possible Human Carcinogen	Testicular tumors inCD-1 rats, Sprague-Dawley rats & Long-Evans Hooded rats

4. Subchronic and Chronic Toxicity

a) Subchronic Toxicity

In a 28 day study with mice (MRID NO. 40535701), tefluthrin (90.4% a.i.) was administered in the diet to Alderly Park albino mice (15/sex/dose) at dose levels of 0, 25, 75, 200, or 400 ppm (calculated by the reviewer to be the equivalent of 0, 3.75, 11.3, 30.0, or 60.0 mg/kg/day) for 28 days. There were no treatment-related changes in clinical condition, gross pathology, histopathology, hematology, or organ weights (testes, kidney, brain, liver). Food consumption data could not be interpreted because there was considerable food wastage in all groups. Body weight gains for the high-dose animals were significantly reduced (↓19-40%) at Weeks 1-4 compared to the controls. In addition, the final body weights of the females were significantly reduced by 10.7%. The LOAEL is 400 ppm (equivalent to approximately 60 mg/kg/day) based on decreased body weight gains in both sexes and final body weights in females. The NOAEL is 200 ppm (equivalent to approximately 30 mg/kg/day). The study supports the selection of 400 ppm (60 mg/kg/day) as the top dose for a lifetime study in the same species.

In a 21-day study with rats (MRID NO. 40180001), tefluthrin (96.5% a.i.) dissolved in acetone was administered in the diet to Alpk:APfSD rats (10/sex/dose) at dose levels of 0, 25, 100, or 400 ppm (calculated by the reviewer to be 1.25, 5, or 20 mg/kg/day) for 21 days. There were no treatment related deaths and no treatment related changes noted in the clinical observations, and the gross pathology and microscopic data. In addition, no neurological signs were noted and none of the serum electrolytes were affected. In the high-dose females, decreases in body weight (↓8%), body weight gain (↓91%), and food consumption (21%) were observed. Also observed were elevated levels of urea (↑11%; $p<0.05$), white blood cells (↑33%), lymphocytes (↑26%), and decreased platelet count (↓13%). Increased absolute (↑9-16%; $p\leq0.05$) and relative (↑6-13%; $p\leq0.05$) liver weights were observed in all dosed males. Elevated cholesterol (↑25%; $p<0.05$) and increased levels of urea (↑9%; $p<0.05$) and neutrophils were observed in the high-dose males. The LOAEL for females for this 21-day oral toxicity study is 400 ppm (equivalent to approximately 20 mg/kg/day) based on decreased body weight gain, decreased platelet counts, and increased WBC and lymphocytes in the high-dose females. The NOAEL for females is 100 ppm (equivalent to approximately 5 mg/kg/day). The NOAEL in males was not observed.

In a 90-day study with rats (MRID NO. 40141304), tefluthrin (90.4% a.i.) was administered in the diet to Alpk/Ap rats (20/sex/dose) at dose levels of 0, 50, 150, or 350 ppm (calculated by reviewer to be equivalent to approximately 2.5, 7.5, or 17.5 mg/kg/day) for 90 days. There were no treatment related deaths and no treatment related changes noted in the food efficiency, clinical observations, gross pathology, and microscopic data. In addition, there were no ophthalmological changes observed that were related to dietary levels of tefluthrin. Body weight gains were reduced ($p<0.01$) in both sexes at the high dose throughout the study. Overall (13 week) body weight gains in the high-dose animals were decreased by approximately 10% ($p<0.01$) and overall food consumption was decreased by 6-8% ($p\leq0.05$) compared to controls.

At 13 weeks, hemoglobin levels in the high-dose males and females and the mid-dose females were decreased (4-6%; $p<0.05$), hematocrit in the high-dose animals were decreased (4%; $p<0.05$), and red cell count was decreased in the high-dose males (5%; $p<0.05$). Plasma cholesterol levels in the mid- and high-dose males were elevated (↑11-18%) and liver weights in the mid- and high-dose males were increased (↑11-13%) at the 13-week interval. The LOAEL for this 90-day feeding study is 150 ppm (equivalent to approximately 7.5 mg/kg/day) based on changes in hemoglobin, cholesterol, and liver weight in the mid-dose animals. The NOAEL is 50 ppm (equivalent to approximately 2.5 mg/kg/day). This 90-day feeding study was classified Supplementary, pending receipt of serum electrolyte data for sodium, calcium, and magnesium. Subsequently in 1989, a 21-day feeding study (MRID NO. 40180001) was submitted and none of the serum electrolytes were affected by dosing with tefluthrin.

b) Chronic Toxicity

Rat

In a chronic/carcinogenicity study (MRID NO. 40141307), tefluthrin (95.1% a.i.) was administered for 24 months in the diet to Alpk:Ap rats (52/sex/dose) at nominal dose levels of 0, 25, 100, or 400 ppm (actual dose levels were equivalent to 1.1, 4.6, or 18.2 mg/kg/day). There were an additional 12 rats/sex/dose that were sacrificed at 52 weeks. There were no treatment related changes noted in the hematology data and ophthalmological examinations. Four males and 5 females from the high-dose group died in the first 3 weeks of the study. Neurotoxicity was noted in the mid- and high-dose animals as an increased response to sound and activity, tremor, abnormal gait, and shaking. Body weight gains for the mid- and high-dose males were decreased significantly for approximately the first 76 weeks of the study; body weight gains for the high-dose females were significantly decreased throughout the study (104 weeks). Food consumption was decreased in the high-dose males for the first 45 weeks of the study and for the first 13 weeks in the high-dose females. Food efficiency was decreased in the mid- and high-dose males (↓43-45%) and in the high-dose females (↓45%). Levels of plasma alanine transaminase were increased in the high-dose females from Week 53 through to the end of the study (↑14-53%; statistically significant at Week 79); at termination, levels in the high-dose males were also increased (↑47). Levels of aspartate transaminase were increased in the mid- and high-dose females from Week 53 through to the end of the study (↑29-105%; statistically significant at Week 79). High-dose males and females had increased liver weights (↑10-11% adjusted for body weight; ↑12-13%; relative to body weight). The chronic LOAEL is 4.6 mg/kg/day based on decreased body weights, and neurotoxicity and clinical chemistry changes in the mid- and high-dose animals. The chronic NOAEL is 1.1 mg/kg/day). This chronic/oncogenicity toxicity study in rats is classified supplementary (pending receipt of a 21-day feeding study reporting serum electrolyte determinations, including magnesium). Subsequently in 1989, a 21-day feeding study (MRID NO. 40180001) was submitted and none of the serum electrolytes were affected by dosing with tefluthrin.

Mice

In a carcinogenicity study (MRID NO. 40161106), tefluthrin (95.1% a.i.) was administered for 104 weeks in the diet to Alpk:AP mice (50/sex/dose) at nominal dose levels of 0, 25, 100, or 400 ppm (actual dose levels were equivalent to 3.4, 13.5, or 54.4 mg/kg/day).

There were no treatment related changes noted in mortality, clinical signs, body weight, food consumption, and hematology data. Urinalysis and ophthalmological examinations were not performed. Although mean liver weights (absolute and relative) were increased in treated males and mean relative liver weights were increased in the high-dose females, there was no evidence of a compound-related effect in any of the examined organs. There were several non-neoplastic changes observed in the mid- and high-dose females including increased incidences of hemangiomatous changes in the uterus and liver necrosis. The chronic LOAEL is 13.5 mg/kg based on hemangiomatous changes of the uterus and liver necrosis observed in the mid- and high-dose females. The chronic NOAEL is 3.4 mg/kg.

5. Mode of Action Studies

No studies available.

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The Committee considered the following for a weight-of-evidence determination of the carcinogenic potential of tefluthrin.

Carcinogenicity

· **Rat: The CARC did not consider the uterine tumors seen in female rats to be treatment-related.** In female rats, there was a significant trend ($p<0.05$) for uterine adenocarcinomas. However, there were no significant pair-wise comparisons of the dosed groups with the controls. The incidences of this tumor at all dose groups was within the historical control range (0-15%) provided by the registrant. Additionally, there were no corroborative non-neoplastic lesions. There was no evidence of carcinogenicity in male rats. The dose levels tested were adequate to assess the carcinogenicity of tefluthrin in rats based on the clinical signs of neurotoxicity and changes in the body weight/body weight gains observed at the high dose in both sexes.

· **Mouse: The CARC did not consider the pituitary gland tumors seen in both male and female mice to be treatment-related.** Male mice had statistically significant trends in pituitary gland adenomas and combined adenomas and/or carcinomas, both at $p < 0.05$. However, there were no significant pair-wise comparisons of the dosed groups with the controls. Female mice had statistically significant trend in pituitary gland pars intermedia adenomas at $p < 0.05$ and a statistically significant trend in pituitary gland pars intermedia combined adenomas and/or carcinomas at $p < 0.01$. There was a statistically significant pair-wise comparison of the 400 ppm dose group with the controls for pituitary gland pars intermedia combined adenomas and/or carcinomas at $p < 0.05$. The incidence of carcinomas at 400 ppm was low (a single carcinoma). Additionally, there were no corroborative non-neoplastic pituitary lesions (hypertrophy/ hyperplasia) to indicate that the tumors were treatment related. The dose levels tested were adequate to assess the carcinogenicity of tefluthrin in mice based on the decreased body weight and body weight gain (both sexes) and the presence of non-neoplastic lesions in the uterus and liver (both sexes) observed at the high dose level.

Mutagenicity

There is no concern for mutagenicity.

Structure Activity Relationship

Tefluthrin has no structural features that would either raise or diminish concern for carcinogenicity.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's Final Guidelines for Carcinogen Risk Assessment (March, 2005), the CARC determined that tefluthrin in "Not Likely to be Carcinogenic to Humans." This classification is based on the lack of evidence of carcinogenicity in male and female mice and male and female rats, and the lack of evidence of mutagenicity.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

Not required.

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